REMARKS

Claims 21-32 are pending. Claims 1-20 and 22 have been canceled. Claims 30-32 have been withdrawn. Claim 21 was amended. No new matter has been introduced by way of these amendments. Reconsideration of the pending claims is respectfully requested.

The Specification

The Office objected to the abstract because it recited the word "said". The abstract has been amended to address this issue.

Applicants have reviewed the specification for the use of trademarks. Appropriate correction has been made.

The Office required that the title of the application be amended. Applicants have amended the title as the Office suggested.

Objection to the Claims

Claim 21 was objected to for reciting a non-elected SEQ ID NO: 4. This claim has been amended to delete reference to this subject matter. Applicants reserve the right to pursue this subject matter in a continuation or divisional application.

Supplemental Information Disclosure Statement

Applicants discuss a number of research articles which are cited to establish that the FDF03 protein is recognized by those of ordinary skill in the relevant art as being an inhibitory receptor. Applicants submit herewith a supplemental Information Disclosure Statement (IDS) to make these references part of the official record and request consideration of the IDS.

The Invention is Supported by a Credible, Specific and Substantial Utility

Claims 21-29 were rejected under 35 U.S.C. § 101 because the claimed invention allegedly was not supported by either a credible, specific, or substantial asserted utility or a well established utility. In particular, the Office alleged that novel biological molecules lack a well-established utility and must undergo extensive experimentation to determine their function.

Applicants have asserted a number of uses for the claimed subject matter which satisfy the exceedingly low burden raised by the law and the Constitution. Once a utility has been asserted, it is the Office's initial burden to establish whether it is more likely than not that a skilled artisan would consider an asserted utility to be credible, specific and substantial. *See, In re Rinehart*, 531, F.2d 1048, 1052 (CCPA 1976).

In contrast to the burden placed upon the applicant to assert a credible, specific and substantial utility, the burden on the Office is much higher. For example, "[t]o violate [35 U.S.C. §] 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992)(emphasis added). As discussed in the M.P.E.P. at section 2107.01, situations where an invention is completely inoperative are rare and examples where the rejection has been upheld on appeal are rarer still. As discussed below, Applicants respectfully submit that the Office has not met their burden in articulating a lack of utility because of the credible, specific and substantial teachings provided in the specification and the state of the art at the relevant point in time.

Asserted Utilities

The claimed subject matter is useful as a diagnostic and therapeutic target on myeloid cells derived from hematopoietic stem cells, the activity of which contributes to a variety of disease states. *See, e.g.*, Specification at page 68, line 22 to page 69, line 16. The FDF03 protein is useful as a diagnostic marker. For example, the specification teaches that the FDF03 protein is a marker on monocytes cells, which are myeloid cells and are derived from hematopoietic stem cells. *See, e.g.*, Specification at page 54, lines 16-22. Thus, the FDF03 protein can be used as a target on monocytes to identify such cells when they infiltrate a particular tissue.

The FDF03 protein is also useful as a therapeutic target. The specification asserts that the FDF03 protein can be used to regulate the activity of hematopoietic cells which play a role in the regulation immunological responses. *See, e.g.*, Specification at page 68, line 37 to page 69, line 3. Applicants provide herewith as Exhibit A, a copy of the declaration by Dr. Joseph H. Phillips, which was submitted in a related case (U.S. Application No. 10/290,631). Dr. Phillips' declaration shows that antibodies against the FDF03 protein were effective to regulate (*i.e.*, prevent) the degranulation of mast cells, which are immunologically active cells derived from hematopoietic stem cells. This data supports Applicants' assertion that the FDF03 protein has therapeutic utility.

The Invention is Useful as a Marker for Myeloid Cells

Applicants assert that the FDF03 protein is useful to identify cells of myeloid lineage, for example, monocytes and dendritic cells in particular. The specification discloses that mRNA encoding the FDF03 protein was highly restricted to dendritic cells and a B lymphocyte cell line, JY. Specification at page 88, line 29 to page 89, line 4. The results of the Northern blot analysis disclosed in the specification are sufficient to indicate to one of ordinary skill in the art that the FDF03 protein is more likely than not useful as a diagnostic marker for identifying dendritic cells.

Applicants further note that antibodies raised against the FDF03 protein have been shown to bind specifically to dendritic cells. Specification at page 87, lines 26-27. The restricted expression of the claimed protein is further confirmed by the work of Fournier, et al., attached as Exhibit B. **Fournier, et al. (2000) *J. Immun.* 165(3):1197-1209**. Fournier, et al. described the expression of FDF03 protein as being restricted to myelo-monocytic origin, including dendritic cells. **Fournier, et al. (2000) *J. Immun.* 165(3):1197, 1202, col. 1.** Applicants submit that, based on the data discussed in the specification and the work by Fournier, an artisan of ordinary skill in the relevant art would more likely than not believe that the diagnostic utility asserted for FDF03 was credible, substantial and specific.

When Applicants made this argument in a related case, the Office rejected it, alleging that the asserted diagnostic utility was not sufficient to satisfy the statute in the absence of disclosure relating to the biological activity of the claimed protein. Applicants respectfully disagree. While a novel protein whose function is unknown may lack utility, it is not a requirement of the statute that

its function be know for that protein to have some use which is credible, substantial and specific. The FDF03 protein is useful as a diagnostic marker with which one of ordinary skill in the relevant art can use to identify monocytes in a sample. As such, the biological function of the protein is completely irrelevant to the question of whether the protein itself is sufficiently useful to justify the granting of a U.S. patent.

FDF03 is an Inhibitory Receptor

The FDF03 protein is an inhibitory receptor of the immunoglobulin superfamily which is expressed by human dendritic and other cells of myeloid lineage. **Fournier, et al. (2000) *J. Immun.* 165(3):1197-1209**. The analysis of FDF03 was centered on the cytoplasmic tail of the protein which contains two immunoreceptor tyrosine-based inhibitory motif (ITIM)-like sequences. The consensus sequence found in the C-terminus of the protein was originally deduced from several receptors known to bind to the carboxyl-terminal SH2 domain of the protein tyrosine phosphatase SHP-1, which defines all immunoreceptors including NK cells, B cells, and monocyte and dendritic cell inhibitory receptors. **Mousseau, et al. (2000) *J. Biol. Chem.* 275(6): 4467, second column, lines 9-16 (Exhibit C)**[1].

SHP-1 and SHP-2 are a Src homology 2 (SH2) domain-containing protein tyrosine phosphatases. *See,* **Kui, QU (2000) *Cell Research* 10:279-288 (Exhibit D)**. SHP-1 is primarily expressed in hematopoietic cells and controls intracellular phosphotyrosine levels in lymphocytes. SHP-2 is ubiquitously expressed in various tissues and cell types. SHP-1 has been proposed as a candidate tumor suppressor gene in lymphoma, leukemia and other cancers, as it functions as an antagonist to the growth-promoting and oncogenic potentials of tyrosine kinase. **Wu, et al. (2003) *Gene* 306:1-12 (Exhibit E)**. SHP-2 has been implicated in diverse signaling pathways including those initiated by growth factors such as PDGF, EGF, IGF-1, cytokines such as IL-3, GM-CSF, and EPO, as well as insulin and interferon. **Kui at 279.** SHP-2 appears to be involved in a variety of signal transduction processes, such as the Ras-Raf-MAP kinase, Jak-Stat, and PI3 kinase pathways.

[1] A homolog of the FDF03 protein (PILRα) was independently characterized by Mousseau, et al. PILRα differs from FDF03 at a single amino acid residue (no. 78).

Id. This functional data indicates that the FDF03 protein plays a role in signal transduction in myeloid cells, such as dendritic cells.

Support for the function of FDF03 goes beyond sequence homology analysis. Fournier, et al. transfected the U397 promyelomonocytic cell line with an expression vector encoding the gene for the FDF03 protein. **Fournier at page 1199, col. 1, line 69 to col. 2, line 10.** When these cells where exposed to pervanadate, the recombinant FDF03 protein was tyrosine-phosphorylated and recruited Src homology-2 (SH2) domain-containing protein tyrosine phosphatase (SHP)-2 and to a lesser extent SHP-1. **Fournier at page 1203, col. 1, line 17 to page 1204, col. 1, line 9.**

In addition to the phosphorylation data, it has been shown that cross-linking of FDF03 inhibited calcium mobilization in response to CD32/FcγRII aggregation in transfected U937 cells. **Fournier at page 1204, col. 1, line 11 to col. 2, line 12.** Release of intracellular calcium is an important intracellular signaling mechanism which can result in cell activation. The inhibition of calcium mobilization in response to CD32 aggregation demonstrates that FDF03 can function as an inhibitory receptor. ***Id.*** Cross-linking of FDF03 did not inhibit GM-CSF-induced monocyte differentiation into dendritic cells, which was interpreted as indicating the possible presence of additional modulatory functions. **Fournier at page 1204, col. 2, line 14 to 1205, col. 2, line 5.** This data is sufficient to demonstrate the biological function of the claimed protein FDF03.

<u>The Function of FDF03 as an Inhibitory Receptor is Art Recognized</u>

Applicants further assert that those of ordinary skill in the art recognize the function of the claimed protein as an inhibitory receptor. The assertion is made based on research papers published by those of ordinary skill in the art which have references the work by Fornier, et al. For example, Luo, et al. (Exhibit F) described FDF03 as a one of a number of immunoglobulin superfamily receptors and compared a novel receptor to the FDF03 protein and other family members. **Luo, et al. (2001) Biochem Bioph Res Co 287:35.** Trowsdale, et al. (Exhibit G) discuss the family of IgSF receptors and speculate that "[t]hese large clusters of receptor and ligand loci must have arisen from prolific duplication." **Trowsdale, et al. (2001) Immunol. Rev. 181:20 at 21.** Clark, et al. (Exhibit H) using their own terminology, describe FDF03 as a member of the immunoregulatory signaling (IRS) family of receptors that play a role in cellular signal transduction in a variety of hemopoietic

cell types. **Clark, et al. (2001) Tissue Antigens 57:415 at 422.** These papers supports Applicants asserted utility that the characterization of the function of the FDF03 protein as a receptor involved in signal transduction propagation in dendritic cells.

The functional role of the IgSF receptor family members (such as FDF03) in signal transduction is based in part on the presence of the ITIM motif and the ability of molecules possessing this motif to bind to SHP-1 and/or SHP-2. de Vet, et al. (Exhibit I) noted that FDF03 contained the ITIM motif, which was known to recruit both SHP-1 and SHP-2. **de Vet, et al. (2001) *J. Biol. Chem.* 276(45): 42070.** Sweeney, et al. (Exhibit J) acknowledge that FDF03 binds to SHP-1 and/or SHP-2. **Sweeney, et al. (2005) *Biochemistry* 44:14932.** Another group, referencing the work of Mousseau, et al., noted that FDF03 contained two ITIM motifs in its cytoplasmic tail, and identified it as a putative inhibitory form. **Hawke, et al. (2001) *PNAS* 98(24): 13832 at 13837** (Exhibit K). Tenca, et al. (Exhibit L) acknowledged that FDF03 plays a role in ITIM signaling. **Tenca, et al. (2005) *J. Immunology* 174:675.** Xu, et al. (Exhibit M) noted FDF03 as a member of a class of recently discovered ITIM-bearing receptors which play a role in "signal transduction pathways and subsequent cellular responses." **Xu, et al. (2002) Biochem. Bioph. Res. Co. 93:820.** Lock, et al. (Exhibit N) acknowledge the nature of FDF03 as an inhibitory receptor on dendritic cells. **Lock, et al. (2004) Immunobiol. 209:199 at 204.** Kikuchi-Maki, et al. (Exhibit O) described FDF03 as an example of a negative signaling receptor. **Kikuchi-Maki, et al. (2003) *J. Immun.* 171:3415-3425.** Toyama-Sorimachi, et al. (Exhibit P) recognize the FDF03 protein as an inhibitory receptor. **Toyama-Sorimachi, et al. (2005) *J. Immun.* 174:4621 at 4622.** The ability of FDF03 to inhibit Ca^{2+} mobilization triggered by the low-affinity receptor for IgG (FcγRII) was acknowledged by Colonna (Exhibit Q). **Colonna, M. (2003) *Nature Reviews Immunology* 3:445 at 446.**

Applicants have cited 14 different papers which regard the FDF03 protein as an inhibitory receptor on dendritic cells. In view of this, Applicants submit that more than an adequate amount of data has been provided to the Office which demonstrates the useful role of the FDF03 protein as a diagnostic marker on monocytes. On the basis of this showing alone, Applicants request that the present lack of utility rejection be withdrawn.

The Invention is Useful to Inhibit Mast Cell Degranulation

In addition to its usefulness as a marker of myeloid-derived cells, the claimed protein is useful as a therapeutic target of compositions which regulate the immune responses of cells derived from hematopoietic stem cells. Specifically, the declaration of Dr. Phillips (Exhibit A) provides data indicating that antibodies against the FDF03 protein inhibit the degranulation of mast cells. Mast cells are immunologically active cells derived from myeloblasts, as are monocytes and dendritic cells. Myeloblasts are in turn derived from hematopoietic stem cells.

The specification does not explicitly discuss mast cells regulation. However, the specification does recognize that the disclosed proteins play a role in the regulation of immunological responses produced from immune cells derived from hematopoietic stem cells. *See, e.g.*, Specification at page 68, line 37 to page 69, line 3. Because mast cell degranulation is an immunological response that can be inhibited by antibodies against the claimed protein, evidence demonstrating an impact of antibodies against the claimed protein, supports the asserted therapeutic use of this protein. As such, the data provided in the Phillips declaration is probative to the issue of utility. Furthermore, given the demonstrated ability of antibodies against the FDF03 protein to inhibit mast cell degranulation, this data is sufficient to show that the claimed protein has utility. Therefor, the present rejection of the claims should be withdrawn in view of the data provided.

Enablement

Claims 21 and 23-29 were rejected under 35 U.S.C. § 112, first paragraph, allegedly because one skilled in the art clearly would not know how to use the claimed invention. Specifically, the Office has interpreted the word "polypeptide" as including fragments of the claimed protein. Applicants have amended claim 21 to remove the word "fragments" from the claim. As such, claim 21 now recites "[a] substantially pure or isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 2." Because the pending claims no longer encompasses fragments of the claimed sequence, the present rejection has been overcome.

Written Description

Claims 21 and 23-29 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office rejected the pending claims alleging that fragments of the claimed sequence were not adequately described. This rejection is overcome by the amendments discussed above. As such, the rejection should be withdrawn.

Anticipation

Claim 21 was rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Torpey *et al.* (GenBank Accession No. P38928). Claims 21, 23-24, and 29 were also rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Chinnadurai (U.S. 5,858,678).

To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

The pending claims relate to a polypeptide which comprises SEQ ID NO: 2. Neither Torpey, et al. nor Chinnadurai teach the complete sequence of SEQ ID NO: 2. Because the cited references fail to teach all the features of the claimed invention, neither can anticipate that invention. Accordingly, these rejections should be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 140942001311. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

By _____

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